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Organ Transplantation Methods and Major Reasons of Organ Rejection

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Abstract

Organ transplantation is a surgical procedure in which damaged or diseased organ of recipient person is replaced with healthy organ of a donor from live or dead source. organ can be taken from donor up to 24 hours past the termination of heart and can be stored up to 5 years by maintaining the ideal conditions for organ. There are different types of organ transplantation which are auto transplantation, allotransplantation, isotranspalantation and xenotransplantation which are classified on the base of source of organ donor and organ receiver. In case of allotransplantation. In case of allotransplantation and xenotransplantation there are high risk of organ rejection because immune system of receiver does not allow the foreign organ to work properly because foreign organ have specific major histocompatibility complexes on their cell membrane and specific self-antigens recipient immune system recognize this organ as foreign pathogen and recipient immune system activated and show immune response against this foreign organ. Therefore, for allotransplantation and xenotransplantation some immune suppressant drugs are used before organ transplantation that suppress the recipient immune system and allow organ to work normally as original organ. In case of auto-transplantation as MHC and self-antigens are same so there are less chances of organ rejection. Organ transplantation increase the bioethical issues by illegal trading of organs which cause the socio-economic problems in the society and should be banned by the governments.

Key words: organ transplantation, graft rejection, major histocompatibility complex, self-antigen, immunology, immunosuppressant

Introduction

Organ transplantation is a medical procedure in which an organ is separated from one body and positioned in the body of a recipient, to change aninjured or lost organ. The donor and recipient can be at the same position, or organs may be transferred from a donor site to alternativeposition. Organs and tissues that are transplanted within the sameperson's body are known asautografts.Transplants thatperformed among two individuals of the same species are known as allografts. Allografts can either be from a living or dead organism source. effectivelyorgans that have been transplanted containsthe lungs,liver, heart,pancreas,thymus and intestine. Recently, working on head transplantation has been started. Tissues comprise bones, tendons (both stated to as musculoskeletal grafts), heart valves, skin,cornea, veins and nerves. Extensively, the kidneys are most commonly transplanted organs, followed by the liver transplant and then the heart transplant. Cornea and musculoskeletal grafts are the most generally transplanted tissues; these outnumber organ transplants by more than tenfold [18].

Organdonors may be living, brain damaged, or dead through circulatory death[16]. Tissue may be taken from donors who expire of circulatory death, as well as of brain death up to 24 hours past the termination of heartbeat. Unlike organs, most tissues except corneas can be well-maintained and kept for up to five years, its mean that they can be “stored”.Kidney donation from a healthy donor carries very low risks of organ rejection.This canonly be done by selecting a compatible donor, careful surgical removal of kidney and follow up of the donor to confirm the ideal management of unexpected conditions.Transplantation increasesanamount of bioethical problems, together with the meaning of death, when and how permission should be given for transplantation of organ, and payment fortransplantation.Other ethical issues contain transplantation tourism and more largely the socio-economic context in which organ gaining or transplantation may occur.A specific problem is organ trading[17].

Transplantation medication is one of the most interesting and broad areas of recenttreatment.Some of theareas for medical management are the complications of transplant rejection, during which the body has an immune response to the transplanted organ, probably leading to transplant rejection and the requirement to directlyeliminate the organ from the receiver. When possible, transplantrejection can be reduced through serotyping to regulate the most suitable donor-recipient match and by the use of immunosuppressant drugs[10].

History

French experimental surgeon,Alexis Carreldeveloped surgicalprocedures for anastomosingblood vessels, which aided organtransplantation to be carried outeffectively for the first time. Forthis work he wasawarded the NobelPrize in [8]. Mathieu Jaboulay, and the Germansurgeon Julius Dorflerpresented thefull-thickness blood vessel suturing method. Technically effective kidney transplantswere completed firstly not by Carrel but byEmerich Ullmann. In 1902 hedid adog auto-transplant and a dog-to-goat cross-species or xenograft. In 1906, the first two renaltransplants in human were done by Jaboulayby means of a pig donor for one transplant and a goatdonor for the other transplant. Ernst Unger,in 1909 more than 100 kidneytransplants performed in animals by usingmonkeydonors. None of these early humankidney cross-species become successful for morethan a fewdays, and all of the recipient soon died[3].

In 1904, Carrel in Chicago, where he joined with thephysiologist Charles Guthrie. They cooperatedfor 12 months, during this time, theyeffectively transplanted the heart, lung, thyroid, ovary, kidney, and small bowel. Carrel'sachievement with organ grafts was nothooked on a new technique of suturing but onhis usage of wellsuture material and needles hisexcellent technical ability, and his interest with strong antisepsis.In the 1930Leo Loeb, determined that the intensityand timing of rejection of skin homograft inrats was administered by the degree of genetic differenceof donor and recipient. He also statedthat the lymphocytes werethe cause of tissue rejection. It showsthat identicaltwins can accept replaced skin grafts.

In 1933 Yu YuVoronoyachievedthe primary human-to-humankidney transplant.That the kidney was not securedtill6 hours after the donor's expiry and that it wastransplanted across a major blood group incompatibilitycaused for organ transplant failure[3].

Joseph Murray On 23 December,1954, solve the problem of organ rejection by using identical twins as the donor of a humankidney transplant. The victory ofthis transplant had no actualscientificconsequencebecause it is well known for decades that there will be no tissue rejection between two identical twins.

In1959, attentionwas drawn to the usage of such medicationsfor transplantationby Robert Schwartz and William Dameshek. They found a drug that is present in rabbitsthat Mercaptopurine (6-MP)lower the antibody effect to bovinealbumen.In 1960, they described that the drug mostlyprolonged the life span of skin homografts. In 1960 RoyCalne, in London, observed fromthese researches, he tested the result of 6-MPon rejection ofkidney of dog homografts andnoted that it significantly increased their life span[3].

Types of transplantation

There are four major types of transplantations based on the source of donor organ mention in the **figure 1**.

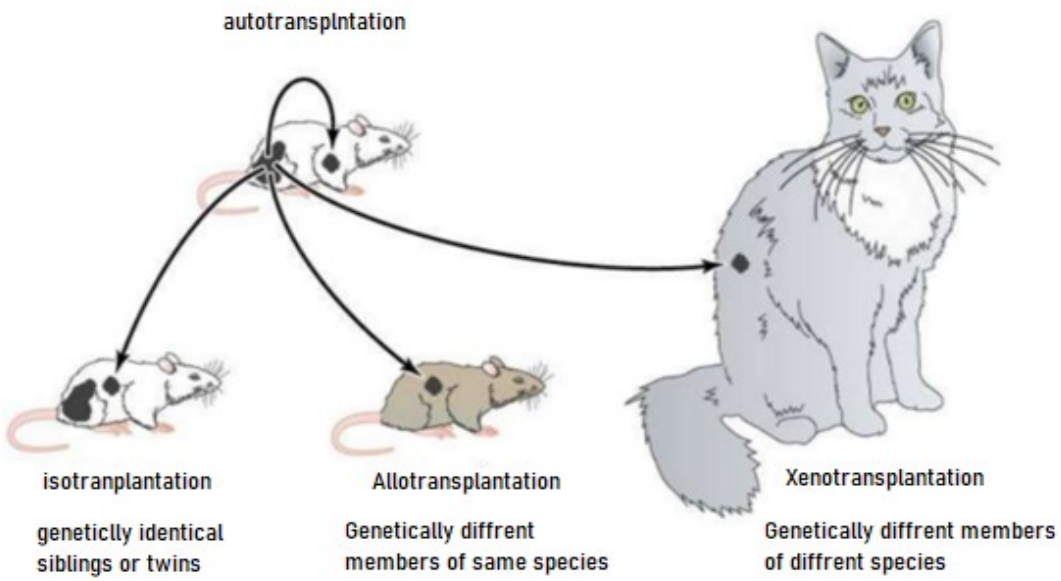

Figure 1: Types of transplantations; Auto-transplantation, Allotransplantation, iso-transplantation and Xenotransplantation.

Auto-transplantation

Auto-transplantation is the surgical procedure in which tissues, organ or even sometypes of structural protein are transplanted from one part of body to a different part of body in the same person. Mostly this is done with such parts of body where tissues having surplus amount and tissues can be regenerated, or tissues more urgentlyrequiredsomewhere else. Examples include skin grafts and bone graft etc.Occasionally an autograft is done to remove the tissue and then operate it or the patient before recurring it, examples include stem cell autograft and storing blood in advance of surgery. A common example is the removal of a piece of bone (usually from the hip) and its being ground into a paste for the reconstruction of another portion of bone[15].

Bone Auto-graft

Bone grafting is a surgical techniquein which some type of missing bones or bones with acute fracture that have little chances of cure and can cause significant health risk to the patient. Some kind of small or acute fractures can be cured but risky for large fractures like compound fractures.Bone usually has the capability to regenerate entirely but needs a very minor fracture space or some sort of support to do so. Bone grafts transplantationcould be autologous it means bone picked from the patient's itself body, mostly from the iliac crest, bone grafts may be allograft bone part from dead individual source, or synthetic which are mostly made from hydroxyapatite or other naturally present compounds and biocompatible sources with analogousstructuralfeatures of bone. With the passage of few month artificially grafted bone replaced as natural bone heals[5].

A negative aspect of autologous grafts is that an extra surgical site is needed, in effect additional potential site for post-operative pain and problems. An autograft may also be achieved without a solid bony structure, for example by means of bone reamed from the anterior superior iliac spine. In this case there is no osteoconductive action only there is an osteo-inductive and osteogenic action, though, as there is no solid bony structure.There is some condition in which block of graft can also be used. block graft, in which a small block of bone is positioned whole in the area where graft is placed. When a block graft will be attained, autogenous bone is the most idealas there is less hazard of the graft rejection as the graft taken from the individual's own body[12].

Autologous bone is classicallycollected from intra-oral sources as the chin or extra-oral sources as thefibula, the iliac crest, the mandible the ribs, and even portions of the skull.Chin gives a great amount of cortico-cancellous autograft and easy approachamongst all the intraoral positions. It can be easily collectedunder normal conditionswith the help of local anesthesia. Closeness of the donor and receiverpositionslessen operative cost and time.

Allotransplantation

Allotransplantation is the process in which tissue or organ transplanted from one individual to the other individual of the same species. Mostly, in human being allotransplantation of organ or tissue done. Because this transplantation is between two individuals of the same species and having different genetic material. It

has higher chances of transplant to be rejected becauserecipient immune system recognizes external transplanted organ as a foreign pathogen and destroy the graft. The chances of transplant rejection can be measured by the Panel reactive antibody level. Allotransplantationisopposite to the auto-transplantation. In allotransplantation as donor organ or tissue having different genetic makeup and having different antigens and different major histocompatibility complexes (MHC) which recognize donor organ as a foreign pathogen and recipient immune system work for destroying the organ.

One such condition of allotransplantation is that in which donor organ having its white blood cells recognize recipient cells as foreign pathogen and destroy recipient cells this allograft rejection is called Graft-versus-Host Disease (GvHD). Mostly this condition is occurred when bone marrow transplant is done. Because in bone there is a very high concentration of white blood cells which cause allograft rejection[13].

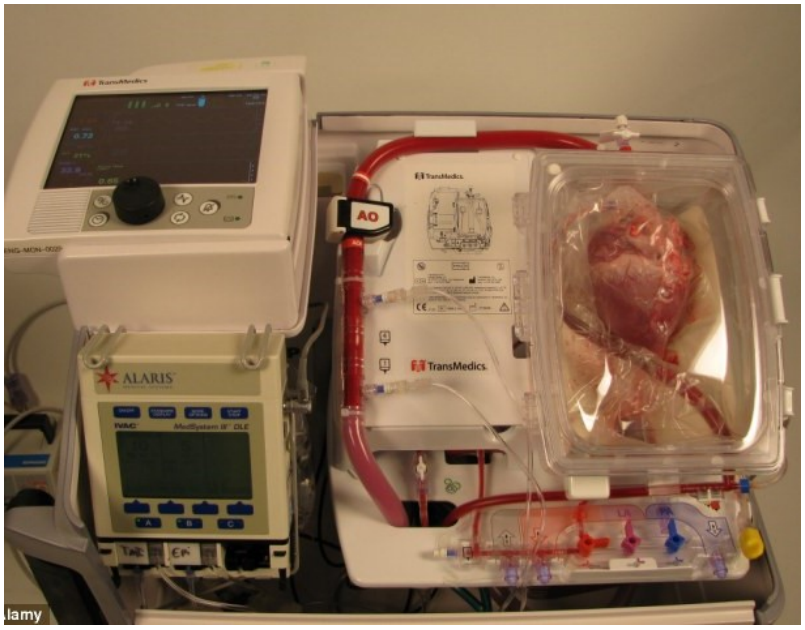

Figure 2: A surgical machine in which suitable condition is provided to store heart for transplantation for long time

A variety of organs and tissues can be used for allografts, together withSkin transplants, Corneal transplants, Heart transplants,Kidney transplants,Liver transplants, Islet cell transplantation, Lung transplantation, Bone allograft and Pancreas transplantation etc.

Heart transplant

A heart transplant, is a surgical transplant processdone on patients with severe coronary artery diseaseor end-stage heart failure.Heart transplantation procedure actually consists of three operations.The first operation is harvesting the heart from the donor who has suffered from brain injury or brain death. Actually,donor is the person with major injury to the head in any case of accident or injury. Victim's other organ except brain is working with the help of medications and other life supports like respirator and other medical devices. Doctors remove heart by doing surgical operations and transported toward recipient by using organ transferring devices shown in the **figure 2**. The second operation is taking away the recipient's injured heart. Eliminating the injured heart may be very difficult or very easy depend on recipient's previous heart surgery. The third operation is the implantation of the donor heart. Unusually, if there are no complications, most patients who have had a heart transplant are home about one week after the surgery. The kindness of donors and their relatives makes organ transplant possible[4].

Iso-transplantation

Iso-transplantation is the subset of allotransplantation in which tissues or organs are transplanted between two organisms of same species and both donor and recipient are genetically identical or identical twins. Isografts are separated from other categories of transplants for the reason that while they are anatomically identical to allografts, they do not stimulate an immune response. Transplant rejection between two such individuals virtually never occurs. As identical twins are also genetically identical and having same major histocompatibility complex (MHC). Therefore, there will be very less chances of organ rejection in recipient. If there will be different major histocompatibility complexes in them as in allograft different organisms of the same species there will be high chances of tissue rejection or organ rejection. No immunosuppressive drugs and other medication are needed. Isograft between identical-twins or genetically identical organism is the successful transplant with no need of immunosuppressive drugs. By using identical twins as a source of organ donor there will be no chances of graft-versus-host disease (GvHD) in which donor organ or tissues destroy the recipient tissues. So, physician mostly preferred that organ donor will be identical twins or genetically identical [3].

Xenotransplantation

Xenotransplantation is the transplantation of organ or tissue from one type of specie to another specie. For example, genetically engineered pigs to human or monkeys to human. Requirement for xenotransplantation isdue to the insufficient availability of organs or tissues. Most of patients dies due to unavailability organ for transplant[9]. Most of recent studies on xenotransplant are become trend to use the organs of other species to cure defected organs of human beings because of insufficient availability of organs for transplant. French surgeon Alexis Carrel developed an attention in cross-species transplantation. In 1907 he wrote that the ideal method of transplantation of organ would be xenotransplantation in future. Firstly, it is necessary to immunize donor specie organ against human serum. It is notable that, more than 100 years ago, Carrel presented what we are today trying to do, we are using genetically modified pigs which are resistant to human immune [8].

However, cross- species transplant is frequently very hazardous category of transplant because of the enlarged risk of non-compatibility, rejection, and sickness carried in the tissue. Effective In a reverse twist, CEO of Ganogen Research Institute EugeneGu is studying how to transplanthuman fetalkidneys and hearts and into different species for upcoming transplantation into human patients to overcome the lack of donor organs.

Safetyand regulatoryaspects

The main concern of xenotransplant study iswhether the organ of donor specie will safe to use or cell cross-species transplant will showharmless from the viewpoint of the transmission of microorganisms or pathogenswith the graft to the recipient.To prevent this, pigs willbe kept under safe conditions and will be testedfor possibly pathogenic microorganisms at consistent intervals. Then the organs which are transplanted from these donors will be safer to transplant. From this viewpoint than an allograft taken from a recentlydead human, where there has been inadequate time tocheck for all possibletransferrablepathogens.With regard to cross-species, greatest concern has linkedto endogenous retroviruses that are existing in the genome of every piggish cell. These endogenous retroviruses will certainly be shiftedwith the donor pig tissues or organ. This possibledangerprovidedsignificantworry some years ago, but it is todayusuallysupposed thatthese are weak viruses and are mostly not problematic, evenin an immunosuppressed receiver[8].

Recent successes in xenotransplantation

In recent few years notablesuccesses have been stated in thenumerousdiverse fields ofxenotransplantation. First, pigs that are geneticallymodified which express many human genes and with removedpig genes cause for hyper acute rejection of transplant have been generated.Second, genetic alterations cause hyper acute rejection of transplant organ someimmunosuppressive drugs are also use which suppress the immune system and body of recipienteasily accept the foreign organ or tissues and resulted in longer survival time of xenotranplant organ.In this way neitherporcine endogenous retrovirus norother porcine microorganisms weretransmitted[9].

Immunology of graft rejection

The entire goal of our immune system or white blood cells is to differentiate between our own healthy cells and infected or pathogenic cells that might their way into our body. So, our body use something called major histocompatibility complex and self-antigen to basically distinguish between out healthy cells and pathogenic cells. The problem actually with grafting or transplantation is that when we transplant some tissues or organ from one individual to another individual there might be very common chances that the grafting tissue or organ have different major histocompatibility complexes (MHC) or different self-antigen from the recipient MHC and self-antigen. If these self-antigens are not compatible or not matching with the recipient antigens then the immune system recognize the graft as a foreign pathogen and produce a defense system to destroy grafting material. Antigens that trigger the immune processin contradiction of theallograft are both minor and major histocompatibility antigens. The whole process of graft rejection is shown in the **figure 3.**

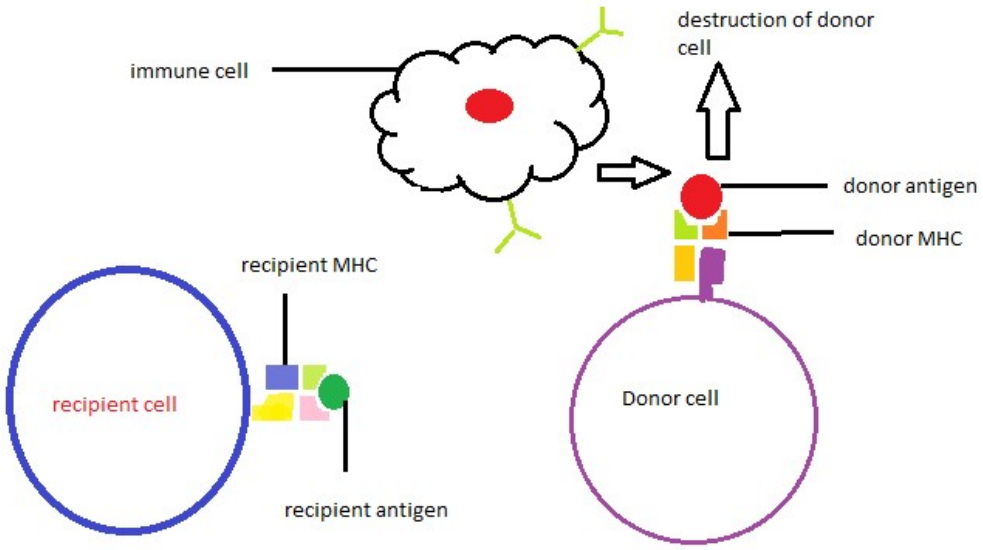

Figure 3: Immune response of recipient immune system against donor cell

In human major histocompatibility present on the 6th chromosome. This chromosome number 6 site expressed and translate human leukocyte antigens which is also known as HLA. HLAare polymorphicin naturecause for making the hardest of responses to allograft tissues or organ. The genes present on 6th chromosomeat thissitetranslate for class I MHC and class IIMHC molecules. Thereason of major histocompatibility complexmolecules is to showexterior antigens for T cells.T cell receptor which is also known asTCR present on the out-side of the T-cell attach with apeptide bond of the major histocompatibility complex (MHC) molecule presenton the externalto the antigen presenting cell. CD8 T cellsrecognize peptide bonds of MHC class I complexes. MHC class 1 almost present on the outer wall of all nucleated cells. CD4 T cells find peptide bonds of MHCcomplexof class II. MHC of class II molecules arepresent on the surface of antigen presenting cells, but expression can be showed onmany cell classeswhen activation[11].

Graft rejection

When tissue or organ from genetically different organism is transplanted it has much higher chances of rejection by the host organism immune system of recipient body attacks anything that it recognizes as being foreign or pathogenic. When MHC of specific self-antigen of donor ransplant tissue cells do not compatible with recipient cell, then recipient immune system creates defensive system against allograft organ. White blood cells recognize the self-antigen present on MHC complex presenting out-side the

grafted organ. When WBC's do not find self -antigens of MHC it stimulates the production of cytotoxic T-cell that will bind to the grafted organ and destroy it. Alloantigen recognition can happenwith two differentdirect pathway and indirect pathway, direct pathway of allorecognitiondesignates the capability of T cells todirectly find non-self MHC molecules present on the donor cell membrane. Indirect pathway is the capability of T cells to find MHC of donor that further managed and present peptides by self-MHC molecule

Role of Major Histocompatibility Complex in graft rejection

The ability of immune system to recognize the body's own cells and grafted cell that are transplanted from other organisms of same species in case of allotransplantation and from other species in case of xenotransplantation depends on the protein markers that are known as major histocompatibility complex (MHC) which are present on each type of cells. In humans these protein complexis called human leukocyte antigen. There are two type of protein complexes present on cell membrane. One is major histocompatibility complex I (MHC I) and other is major histocompatibility complex II (MHC II)[2].

Role of Major histocompatibility complexes I (MHC I) in graft rejection by direct pathway

MHC I protein complex is the protein which present on the membrane of nucleated cells. These cells are used to differentiate between body's own cells and foreign organ or tissue that is transplanted from another organism. Recipient cell produce some types of protein that binds to the cleft portion of MHC class I complex which is known as self-antigen. This self-antigen recognized by the leucocytes or white blood cells that are the cell of immune system and protect body from foreign pathogens. When leucocyte approaches the self-antigen and recognize self-antigen as a it leaves the cell as a body own cell. In condition when allograft or xenograft is transplanted, foreign organ or tissue having different types of antigen present in the cells as compare to the self -antigen of individual own tissue this protein is known as non-self-antigen. When leucocytes or WBCs bind with non-self-antigen it recognizes cell as foreign tissue or pathogen and initiate immune system /to produce immune response against the grafted organ and automatically destroy the grafted organ as shown in the **figure 4**[2].

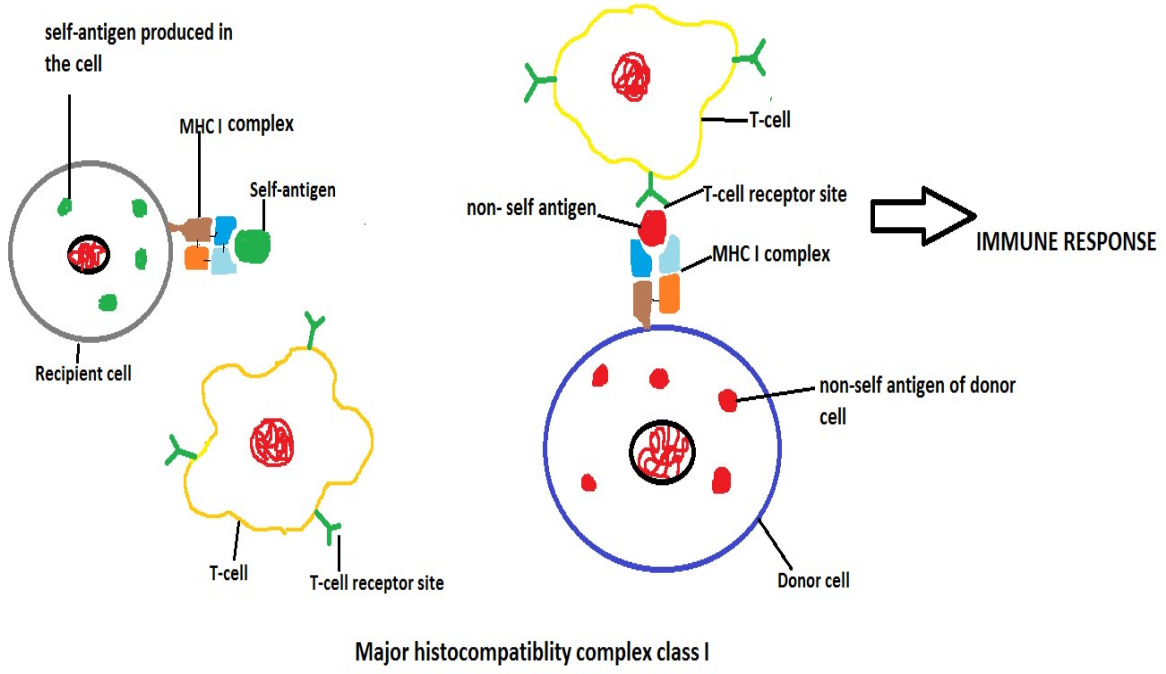

Figure 4: this figure shows the role of major histocompatibility complex in donors graft rejection

Role of Major Histocompatibility Complex II (MHC II) in graft rejection by indirect pathway

Major histocompatibility complex II is the protein complex present only on specific immune cells like B-lymphocytes, macrophages, dendritic cells and some T-lymphocytes. The main function of these protein complex is to communicate between immune cells with one another. In case of allograft transplantation and xenograft transplantation as there is different antigen present on the MHC complex of donor cell membrane. Dendritic cells of recipient tissues having major histocompatibility complex II (MHC II Complex) uptake allogenic antigen or peptide from donor cell MHC complex and further processed to expose on the recipient cell MHC II Complex. When allogenic antigen or peptide is exposed on MHC II complex it produces specific type of chemical known as interleukin 1 which activate the helper-T-cell. Helper-T-cells are the specific type of T-lymphocytes. Activated helper-T-cells have specific sites that recognize the allogenic antigen and release interleukin 2. This chemical move toward B-lymphocyte and T-lymphocytes and force these cells to differentiate in their specialized cells. B-lymphocytes differentiate into memory B-cells as well as plasma cell. While T-lymphocytes differentiate into cytotoxic-T-cell. These cytotoxic-T-cells have specific antibodies on their membrane that produce such types of proteins that digest

the donor organ and then it is responsible for tissue rejection. Plasma cells produce such types of antibodies that recognize the MHC II complex [1].

Infections

The donated tissues or organ may contain dangerous pathogens such as HIV, hepatitis B, syphilis and many others. Nowadays this problem is very rare because organs are routinely checked for these pathogens before donation. When xenotransplantation is done between two organisms of different species then there will be the chances of transfer of infectious pathogens from donor to host cells. In case of xenograft between pigs and human endogenous retroviruses which are present in pig cell are transferred which can cause infection in grafted cell and cause rejection [8]Afzali.In case of allotransplantation between two organisms of same specie has been related with thetransfer of viruses and other pathogens that can cause infection in allograftin the host, includingviruses such as the hepatitis C, hepatitis B, human immunodeficiency virus (HIV), West Nile virus, rabies virus, hepatitis E virus (HEV), fungi such as Aspergillus, bacteria suchas Treponema pallidum and many others parasites. Accurate observing for transferable pathogens in the host and removing of tissues from the donors will be compulsory by the monitoring authorities for a long period of time [9].

Solution of rejection of organs

Tissue typing

the process which involves the determination of Major Histocompatibility complex antigens of the host individual and find a donor that is most compatible.

Immunosuppression

Chemical agents can be used to interfere with the production of host white blood cells. This suppress the immune system and prevents it from mounting an attack on the graft.

Unfortunately, these chemicals can also affect other cells of the host individual. In addition, suppressing the immune system can also lead to infection and cancer.

Conclusion

Before organ transplantation make sure that tissues of donor and recipient are genetically matched if tissues do not match there will be the high risk of organ rejection. Major histocompatibility complex plays

important role in organ rejection and organ selection. MHC have self-antigen. If recipient immune system compatible with the organ's MHC and self-antigen it does not show any reaction against foreign organ if MHC and self-antigen of organ is not compatible with immune system it shows degenerative effects and organ is rejected. Before organ transplantation tissue typing test is done to match donor and receiver tissues or some immune suppressant drugs are used throughout the life.

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